We claim:

1. A computer-implemented method of searching for the unit cell parameters of a crystalline solid form of a compound, which comprises:

performing a Monte-Carlo algorithm to identify one or more sets of values of unit cell parameters that produce calculated X-ray powder diffraction peak positions within a predetermined variance of the peak positions measured from an actual pattern of the crystalline solid form;

where the Monte-Carlo algorithm generates potential unit cell solutions beginning with a specified symmetry and with a specified volume within the confines of an estimated volume of the compound, and iteratively reduces the symmetry and/or increases the volume of the potential unit cell solution until identifying the one or more sets of values of unit cell parameters.

2. A method as claimed in claim 1, where the Monte-Carlo algorithm generates potential unit cell solutions beginning with the highest possible symmetry.

3. A method as claimed in claim 1, where the Monte-Carlo algorithm generates potential unit cell solutions beginning with the Orthorhombic symmetry.

4. A method as claimed in claim 1, where the Monte-Carlo algorithm generates potential unit cell solutions beginning with the lowest possible volume.

5. A method as claimed in claim 1, where the Monte-Carlo algorithm generates potential unit cell solutions characterized by at least their symmetry and multiplicity, and which comprises increasing the volume of the potential unit cell solution by increasing the multiplicity of the potential unit cell solution.

6. A method as claimed in claim 1, where the Monte-Carlo algorithm generates potential unit cell solutions characterized by at least their symmetry and the number of molecules per asymmetric unit cell, and which comprises increasing the volume of the potential unit cell solution by increasing the number of molecules per asymmetric unit cell of the potential unit cell solution.

7. A method as claimed in claim 1, where the Monte-Carlo algorithm generates potential unit cell solutions characterized by at least their symmetry and multiplicity and the number of molecules per asymmetric unit cell.

8. A method as claimed in claim 7, which comprises increasing the volume of the potential unit cell solution by increasing the multiplicity and number of molecules per asymmetric unit cell of the potential unit cell solution.

9. A method as claimed in claim 1, where the Monte-Carlo algorithm generates potential unit cell solutions within the confines of estimated molecular dimensions of the compound.

10. A method as claimed in claim 9, where the limits on lattice parameters of the potential unit cell solutions are determined according to formulas I and II:

$$Ds - 2 < Cs < Ds + 5 \qquad (I)$$
$$Ch > Dh - 3 \qquad (II),$$

where

Ds is the shortest molecular dimension,

Cs is the shortest lattice parameter,

Dh is the longest molecular dimension,

Ch is the longest lattice parameter, and

Ds, Cs, Dh and Ch are in Å.

11. A method as claimed in claim 9, where the limits on lattice parameters of potential unit cell solutions are determined by molecular packing energy minimization for specific space group symmetry operators and hydrogen bond networks.

12. A method as claimed in claim 1, where, for potential unit cell solutions characterized by a number of molecules per asymmetric unit cell of two or more, the potential unit cell solutions are further characterized by a side-by-side, head-to-toe or top-and-bottom stacking of any given molecules in the unit cell.

13. A method as claimed in claim 12, which comprises assigning a frequency to each possible stacking configuration of the molecules, and where the number of potential unit cell solutions generated for each possible stacking configuration is proportional to the assigned frequency of the stacking configuration.

14. A method as claimed in claim 1, which comprises:

providing an estimated volume and, optionally, estimated molecular dimensions of the compound;

providing a potential unit cell solution characterized by at least its symmetry and multiplicity and the number of molecules per asymmetric unit cell;

generating one or more sets of values of unit cell parameters confined by the volume and, if applicable, molecular dimensions of the compound and by the provided potential unit cell solution;

calculating the X-ray powder diffraction peak positions associated with each of the generated sets;

calculating for each generated set the variance between the calculated peak positions and the peak positions measured from an actual X-ray powder diffraction pattern of the crystalline solid form;

identifying and storing any generated set of values of the unit cell parameters when the variance calculated for the set is below a predetermined value; and

rejecting any generated set of values of the unit cell parameters when the variance calculated for the set is above the predetermined value.

15. A method as claimed in claim 1, which comprises one or more steps of reducing the symmetry of a potential unit cell solution while maintaining the volume of the potential solution.

16. A method as claimed in claim 11, which comprises one or more steps of changing the side-by-side, head-to-toe or top-and-bottom stacking of any given molecules in a potential unit cell solution.

17. A method as claimed in claim 1, where the calculation of the variance between the calculated and measured X-ray powder diffraction peak positions comprises a first pass calculation of a crystallographic factor R^1.

18. A method as claimed in claim 17, which comprises rejecting any generated set of values of the unit cell parameters when the crystallographic factor R^1 calculated for that set is above a predetermined value of R^1.

19. A method as claimed in claim 1, where the calculation of the variance between the calculated and measured X-ray powder diffraction peak positions for one or more sets of values of the unit cell parameters comprises a first pass calculation of a crystallographic factor R^1 below a predetermined value of R^1, and which further comprises

generating a predetermined number of additional sets of values of unit cell parameters proximate to each of the initially-generated sets that produced the first pass calculation of R^1 below the predetermined value of R^1;

calculating the X-ray powder diffraction peak positions associated with each of the additional generated sets;

calculating for each additional generated set the variance between the calculated peak positions and the peak positions measured from the actual X-ray powder diffraction pattern of the crystalline solid form;

identifying and storing any initial or additional generated set of values of the unit cell parameters when the variance calculated for the set is below a predetermined value of a crystallographic factor R^2, where $R^2 < R^1$; and

rejecting any generated set of values of the unit cell parameters when the variance calculated for the set is above R^2.

20. A method as claimed in claim 19, which comprises generating the additional sets of values of the unit cell parameters within ± 0.25 Å of the initially-generated unit cell lengths and within ± 1 degree of the initially-generated unit cell angles.

21. A first refinement method, which comprises:
providing stored results obtained from the method of claim 1;
calculating the X-ray powder diffraction pattern of each stored search result;
comparing each calculated pattern to an actual X-ray powder diffraction pattern of the crystalline solid form; and
ranking the results by the similarity of their calculated patterns to the actual pattern of the crystalline solid form.

22. A method as claimed in claim 21, which comprises selecting and storing a predetermined number of non-duplicate results that produce calculated patterns having the fewest peaks and a sum-squared error with the actual pattern below a predetermined value.

23. A second refinement method, which comprises:
providing the results obtained from the method of claim 22; and
determining the space group and parameter positions for each unit cell that produce a calculated X-ray powder diffraction pattern having the closest fit to the actual pattern of the crystalline solid form.

24. A method as claimed in claim 23, which comprises determining the space group and parameter positions for each unit cell by a method which comprises:

providing a predetermined number of potential space group solutions and potential positionings of the unit cell parameters;

calculating the X-ray powder diffraction pattern associated with each of the generated space group solutions and positionings of the unit cell parameters; and

selecting the space group solution and positioning of the unit cell parameters that produces a calculated X-ray powder diffraction pattern that is the closest fit with the actual pattern of the crystalline solid form.

25. A method as claimed in claim 24, where the closest fit with the actual pattern of the crystalline solid form is the lowest sum-squared error between the calculated and actual patterns.

26. A third refinement method, which comprises:

providing results obtained from the method of claim 23;

calculating the electron density map of the unit cell associated with each of the results;

accepting any result that produces a valid electron density map of the unit cell; and

rejecting any result that does not produce a valid electron density map of the unit cell.

27. A method as claimed in claim 26, which comprises calculating the electron density map of the unit cell of each result by a method which comprises:

generating a predetermined number of potential electron density node distributions;

calculating the X-ray powder diffraction structure factors associated with each of the generated electron density node distributions;

selecting the electron density node distribution that produces calculated X-ray powder diffraction structure factors that are the closest fit with X-ray powder

diffraction structure factors extracted from the unit cell corresponding to that result.

28. A fourth refinement method, which comprises:

providing accepted results obtained from the method of claim 26;

calculating the X-ray powder diffraction pattern associated with each result;

comparing the calculated X-ray powder diffraction patterns with a control pattern; and

selecting the result that produces a calculated X-ray powder diffraction pattern that is the closest fit with the control pattern.

29. A method for determining the unit cell parameters of a crystalline solid form of a compound, which comprises:

providing a plurality of sets of unit cell parameters, one of which describes the correct values of the unit cell parameters of the crystalline solid form or values of the unit cell parameters that are proximate to the correct values of the unit cell parameters of the crystalline solid form; and

performing a refinement method to identify the solution to the unit cell parameters of the crystalline solid form, which comprises:

calculating the X-ray powder diffraction pattern of each stored search result;

comparing each calculated pattern to an actual X-ray powder diffraction pattern of the crystalline solid form;

selecting and storing a predetermined number of non-duplicate results that produce calculated patterns having the fewest peaks and a sum-squared error with the actual pattern below a predetermined value;

determining the space group and parameter positions for the unit cell of each result;

calculating the electron density map of the unit cell associated with each of the results;

accepting any result that produces a valid electron density map of the unit cell; and

rejecting any result that does not produce a valid electron density map of the unit cell.

30. A system for searching for the unit cell parameters of a crystalline solid form of a compound, which comprises a central processing unit programmed to execute the method of claim 1 and a memory to store program code executed by the central processing unit.

31. A system for determining the unit cell parameters of a crystalline solid form of a compound, which comprises a central processing unit programmed to execute the method of claim 29 and a memory to store program code executed by the central processing unit.

32. A computer-readable medium for use on a computer system, the computer-readable medium having computer-executable instructions for performing the method of claim 1.

33. A computer-readable medium for use on a computer system, the computer-readable medium having computer-executable instructions for performing the method of claim 29.

34. A method for distinguishing between crystalline solid forms of different samples of a substance, which comprises:

for each sample, selecting and storing a predetermined number of non-duplicate results of possible solutions to the unit cell parameters obtained from the method of claim 22; and

comparing the predetermined number of non-duplicate results of one sample to those of another sample; and

evaluating the difference between the results to determine whether the different samples represent the same or different crystalline solid forms.

35. A method for distinguishing between crystalline solid forms of different samples of a substance, which comprises:

providing, for each sample, one or more valid electron density maps of the unit cell obtained from the method of claim 26; and

comparing the one or more valid electron density maps of one sample to one or more valid electron density maps of another sample; and

evaluating the difference between the electron density maps between the samples to determine whether the different samples represent the same or different crystalline solid forms.